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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/955,037	WHITAKER ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *3 and 15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on April 4, 2003 has been entered. The claims pending in this application are claims 1-15 with claims 3 and 15 withdrawn from consideration as the result of the restriction requirement. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on April 4, 2003.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 2, 5-9, 12, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (US Patent No. 6,380,377, filed on July 14, 2000) in view of Dahlberg *et al.*, (US Patent No. 5,837,450, published on November 17, 1998).

Regarding claims 1, 7, 12, and 13, Dattagupta taught a hairpin nucleic acid probe comprising a stem region and a loop region wherein the stem region had a restriction enzyme cleavage site (see Figure 1 and columns 3 and 4). The hairpin was covalently attached to a solid support such as a glass as recited in claim 13 by a reactive group (a surface-coupling group as recited in claims 7 and 12) associated with the hairpin probe (see columns 12 and 13). Note that: (1) although a nucleotide sequence complementary to a target nucleotide in the hairpin nucleic acid probe taught by Dattagupta is located within its double stranded segment (see column 1, lines 18-23), the loop region has an ability to form a duplex with a potential target nucleic acid that is different from the target nucleotide taught by Dattagupta under suitable conditions since claim 1 is directed to a nucleic acid probe and a target nucleic acid is not a part of structure of the nucleic acid probe as recited in claim 1; (2) although Dattagupta does not directly show that hybridization of a fully complementary target nucleic acid to the loop sequence of the hairpin probe broke the intramolecular hybridization bonds of the stem structure and removed the restriction site as recited in claim 1, this limitation was considered to be a capability of the hairpin probe since at least one potential target nucleic acid could hybridize with the loop sequence of the hairpin probe and break the intramolecular hybridization bonds of the stem structure and removes the restriction site.

Regarding claims 5 and 6, in example 2, a 48-mer hairpin probe had a Nla III site (4 bp in length) (see column 23) (for NIA III site, see attached 96/97New England Biolabs Catalog, page 42).

Regrading claim 9, one end of the hairpin probe had a spacer groups (see column 12).

Dattagupta does not disclose a hairpin probe with a label on one end of the probe as recited in claims 1, 2, and 8.

Dahlberg *et al.*, taught that 3' of hairpin probe was attached to a solid support, such as an agarose, styrene or magnetic bead while 5' of hairpin probe had a label such as radioactive, fluorescent, and biotinylated label as recited in claim 8. If the hairpin structure was not cleaved, the 5' label remained attached to the solid support. If cleavage occurred, the 5' label was released from the solid support as recited in claims 1 and 2 (see column 17). Therefore, it would be obvious to one having ordinary skill in the art at the time the invention was made that cleavage of the stem sequences of the probe comprising a restriction enzyme site with the restriction enzyme would detach the label from the surface of the solid support as recited in claim 1.

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a hairpin probe with a label on its 5' end as recited in claim 1 in view of the patents of Dattagupta and Dahlberg *et al.*. One having ordinary skill in the art would have been motivated to modify Dattagupta's hairpin probe because the incorporation of a detectable label into a hairpin nucleic acid would enhance direct detection of a hybridization assay, and the simple replacement of one hairpin probe (i.e. a unlabeled probe) from another hairpin probe (ie., a labeled probe) for

constructing an immobilized hairpin probe as recited in claims 12 and 13 would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

4. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (July 14, 2000) in view of Dahlberg *et al.*, (1998). as applied to claims 1, 2, 5-9, 12, and 13 above, and further in view of Kacian *et al.*, (US Patent No. 5,935,833, published on August 10, 1999).

The teachings of Dattagupta and Dahlberg *et al.*, have been summarized previously, *supra*. Dahlberg *et al.*, taught that 5' of hairpin probe had a label such as radioactive, fluorescent, and biotinylated label (see column 17).

Both Dattagupta and Dahlberg *et al.*, do not disclose a hairpin probe having an acridinium label as recited in claim 4.

Kacian *et al.*, do teach a DNA probe having an acridinium label (see example 6 in column 16).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a hairpin probe having an acridinium label as recited in claim 4 in view of the patents of Dattagupta, Dahlberg *et al.*, and Kacian *et al.*. One having ordinary skill in the art would have been motivated to modify a hairpin probe recited in claim 1 because Dahlberg *et al.*, suggested that the label on a nucleic acid was exchangeable (see third paragraph in column 17) and the simple replacement of one kind of label (ie., a radioactive or fluorescent or biotinylated label) from another kind of label (ie, an acridinium label) during the process of constructing a hairpin probe as recited in claim 4 would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

5. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (July 14, 2000) in view of Dahlberg *et al.*, (1998). as applied to claims 1, 2, 5-9, 12, and 13 above, and further in view of Johnson *et al.*, (US Patent No. 6,372,813, filed on June 25, 1999).

The teachings of Dattagupta and Dahlberg *et al.*, have been summarized previously, *supra.* Dattagupta taught that one end of the hairpin probe had a spacer groups. Amines, hydroxyl, thiol, and carboxyl groups were suitable for attaching the extended portion of the spacer to the surface attaching portion (see column 12).

Both Dattagupta and Dahlberg *et al.*, do not disclose to use polythymine spacers as recited in claim 10.

Johnson *et al.*, teach nucleic acids comprising a spacer region. Polythymine was one kind of spacer (see column 6).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a hairpin probe comprising polythymine spacers as recited in claim 10 in view of the patents of Dattagupta, Dahlberg *et al.*, and Johnson *et al.*. One having ordinary skill in the art would have been motivated to modify a hairpin probe recited in claim 1 because the simple replacement of one kind of spacer from another kind of spacer (ie., polythymine spacers) during the process of constructing a hairpin probe as recited in claim 10 would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

6. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (July 14, 2000) in view of Dahlberg *et al.*, (1998). as applied to claims 1, 2, 5-9, 12, and 13 above, and further in view of Beattie (US Patent No. 6,156, 502, priority date: December 19, 1996).

The teachings of Dattagupta and Dahlberg *et al.*, have been summarized previously, *supra*. Dattagupta taught that the hairpin was covalently attached to a solid support such as a glass by a reactive group (a surface-coupling group associated with the hairpin probe (see columns 12 and 13).

Both Dattagupta and Dahlberg *et al.*, do not disclose a hairpin probe having a aminopropanol at its 3' end as recited in claim 11.

Beattie does teach to covalently attach an oligonucleotide having a aminopropanol at its 3' end to a solid support (see third paragraph of column 8 and columns 12 and 13).

Therefore, in the absence of an unexpected result, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made a hairpin probe as recited in claim 11 in view of the patents of Dattagupta, Dahlberg *et al.*, and Beattie. One having ordinary skill in the art would have been motivated to modify the hairpin probe as recited in claim 1 because chemical synthesis of oligonucleotide probes having a aminopropanol at its 3' end using the standard phosphoramidite method was known in the art at the time the

invention was made (see Beattie, column 12, last paragraph) and the simple replacement of one kind of 3' end covalent surface coupling group from another kind of 3' end covalent surface coupling group(ie., 3' aminopropanol) during the process of constructing a hairpin probe would have been, in the absence of an unexpected result, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

7. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dattagupta (July 14, 2000) in view of Dahlberg *et al.*, (1998). as applied to claims 1, 2, 5-9, 12, and 13 above.

The teachings of Dattagupta and Dahlberg *et al.*, have been summarized previously, *supra.* Dattagupta taught that the hairpin probe having 8 bp loop sequences (see column 23).

Both Dattagupta and Dahlberg *et al.*, do not disclose a hairpin probe having 16-25 bp loop sequences as recited in claim 14.

However, in the absence of unexpected results, it would have been obvious to one having ordinary skill in the art at the time the invention was made to have a hairpin probe having 16-25

bp loop sequences as recited in claim 14 in view of patents of Dattagupta and Dahlberg *et al.*. One having ordinary skill in the art has been motivated to modify the hairpin probe recited in claim 1 because optimization of nucleotide number of loop sequence in a hairpin probe would have been obvious to one having ordinary skill in the art at the time the invention was made. One having ordinary skill in the art at the time the invention was made would have been a reasonable expectation of success to optimize nucleotide number of loop sequence during the process of constructing a hairpin probe . Note that where the general conditions of a claim are disclosed in the prior art, it is not inventive, in the absence of an unexpected result, to discover the optimum or workable ranges by routine experimentation. *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

Response to Arguments

In page 5, last paragraph bridging to page 8, fifth paragraph of applicant's remarks, applicant argues that: (1) "[D]attagupta differs from the present in that the method of the reference requires that the portion of the probe sequence that takes part in intermolecular hybridization to the target DNA must be part of the sequence that is involved with the intramolecular hybridization, i.e. the target binding portion must be at least partly located within the stem portion of the hairpin." while "[T]he present invention requires that the nucleotide sequence complementary to the target nucleotide sequence be located solely within the loop region."; and (2) "[I]n the method of Dahlberg et al., the restriction site is formed by annealing complementary molecules to the target nucleic acid. See column 7, lines 17-63. With the present

invention, the complete opposite occurs in that the restriction site is destroyed by annealing the target nucleic acid to the probe. In addition, Dahlberg et al. works by the detection of label following digestion, whereas with the present invention, the label is detected in the undigested probe. Finally, Dahlberg et al. differs from the present invention in the use of a special nucleate that specifically cleaves double-stranded nucleic acid into single-stranded products. The restriction enzyme of the present invention cuts the double strand across both strands, leaving double-stranded products and the present invention relies on the weakness of the cleaved stem structure to remove the portion of the probe containing the label.".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, although a nucleotide sequence complementary to a target nucleotide in the hairpin nucleic acid probe taught by Dattagupta is located within its double stranded segment (see column 1, lines 18-23), the loop region has an ability to form a duplex with a potential target nucleic acid that is different from the target nucleotide taught by Dattagupta under suitable conditions. Second, since claim 1 is directed to a nucleic acid probe, a target nucleic acid argued by applicant is not a part of structure of the nucleic acid probe as recited in claim 1. Furthermore, applicant does not provide an evidence to show why the loop region of the hairpin probe taught by Dattagupta can not hybridize with a potential target nucleic acid that is different from the target nucleotide taught by Dattagupta under suitable conditions. Third, although the hairpin probe taught by Dahlberg *et al.*, is made by a method that is different from present invention and is used for different ways that are different from present invention, since claim 1 is directed to a product (ie., a nucleic acid) and is not directed to a method for

making and using the product, the argument made by applicant is related to a process for making or using. Note that the product is unpatentable even though the prior product is made by a different process since the patentability of a product does not depend on its method of production. *In re Thorpe*, 227 USPQ 964, 966 (Fed. Cir. 1985). Since there is no structural difference between a nucleic acid probe made in view of the patents of Dattagupta and Dahlberg *et al.*, and a nucleic acid recited in claim 1, the rejection is proper. Note that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *In re Casey* , 152 USPQ 235 (CCPA 1967); *In re Otto* , 136 USPQ 458, 459 (CCPA 1963).

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claim is allowed.

10.. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703) 308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (703) 305-1270. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the patent Analyst of the Art Unit, Ms. Chantae Dessau, whose telephone number is (703) 605-1237.

Frank Lu
May 23, 2003

ETHAN WHISENANT
PRIMARY EXAMINER